64

UNRELATED UMBILICAL CORD BLOOD TRANSPLANTATION FROM A SINGLE 4/6 MATCHED UNIT IS AN EFFECTIVE THERAPY FOR CHILDREN WITH MALIGNANT AND NON-MALIGNANT DIAGNOSES: GOOD SURVIVAL, LOW GRAFT FAILURE AND GRAFT-VS-HOST DISEASE IN A SINGLE CENTER ANALYSIS OF 314 PATIENTS

Prasad, V.K.[1], Mendizabal, A.[2], Gill, P.[1], Parikh, S.H.[1], Szabolcs, P.[1], Driscoll, T.A.[1], Page, K.[1], Wood, S.[1], Semmel, D.[1], Martin, P.L.[1], Carter, S.[2], Kurtzberg, J.[1 1] Duke University Medical Center, Durham, NC; [2] The EMMES Corporation, Rockville, MD

Background: Despite millions in unrelated registries, many patients, in particular the minorities can not find a suitable donor. In contrast, with an inventory of 250,000 almost every patient will find a 4/6 cord blood unit (CBU). We summarize a large single center experience utilizing unrelated 4/6 matched CBU in pediatric patients.

Methods: 314 consecutive patients (median age 6.1 years; range 0.5–21.3 years) undergoing myeloablative transplantation at Duke between 08/1993 and 11/2007 with a single 4/6 matched (low resolution for HLA-A and –B and high resolution –DRB1) CBU were studied (median follow-up 6.9 years; range 0.9–15.1 yrs). The patients (63% male; 27% non-Caucasian; 38% CMV seropositive) had malignant (61%; n = 192; de novo and secondary leukemia, lymphoma, MDS, others) and non-malignant (39%; n = 122; metabolic, immunodeficiency, marrow failure; and hemoglobinopathies) diagnoses. In total, 51% were mismatched at one and 49% at two class I HLA loci. The median pre-cryopreserved and reinfused total nucleated cell (TNC) doses were 6.16×10^7/kg (range, 0.86–38.23) and 4.80×10^7/kg (range, 0.54–27.40), respectively. Statistics included Kaplan-Meier, log-rank, and Cox models.

Results: Cumulative incidence (CINC) of neutrophil engraftment (median 26 days) at 42 days was 77.7%(95%CI, 73.0%-82.4%) and of platelet engraftment 50K (median 160 days) at 180 days was 52.1%(95%CI, 46.6%-57.6%). Primary graft failure and autologous recovery occurred in 21 (6.7%) and 10 (3.2%) patients, respectively. The 100-day CINC of acuteGVHD grades III-IV was 13.6%(95%CI, 9.7%-17.5%). CINC of chronicGVHD at 1 year was 13.7%(95%CI, 9.8%-17.6%). The probabilities of overall survival (OS) at 1 year and 3 years were 54.8%(95%CI, 49.1%-60.1%) and 46.6%(95%CI, 40.9%-52.0%), respectively.

Factors affecting OS in Mutlivariate Analysis

	1 year OS		Long-term OS		
	Hazard Ratio	p-value	Hazard Ratio	p-value	Favorable Factors
TNC cryopreserved x 10e7/kg					
< 2.5	1.00		1.00		Cell Dose > 2.5
> 2.5	0.41	0.0003	0.45	0.0005	
HLA B Mismatch					
0 or 1 Mismatch	1.00		1.00		0 or 1 mismatch over
2 mismatch	2.16	0.05	2.02	0.04	2 HLA-B mismatch
Recipient Gender					
Male	1.00		1.00		
Female	1.47	0.03	1.39	0.04	Male Recipient

In multivariate model, 1-year and long-term OS were better in boys, pre-cryo TNC>2.5×10^7/kg, and 0 or 1 compared to 2 HLA-B mismatches. The OS in minority and Caucasian patients was similar. The probability of relapse of malignancy at 5 yrs was 10.1%(95%CI 5.8%-14.4%).

Conclusion: Transplantation using single 4/6 matched CBU is effective and carries low probabilities of graft failure, acute GVHD grades III-IV and chronic GVHD in pediatric patients. Outcomes are similar to those reported with better matched UCB grafts. These results support the use of 4/6 matching CBU for patients lacking matched related and unrelated donors improving access for all patients including the minorities.

65

IMMUNE RECONSTITUTION AFTER GENE THERAPY (GTX) FOR ADENOSINE DEAMINASE DEFICIENT SEVERE COMBINED IMMUNE DEFICIENCY (ADA-SCID)

Sokolic, R.[1], Podsakoff, G.[2], Muul, L.[1], Engel, B.[2], Jagadeesh, J.[1], Garabedian, E.[1], Kesserwan, C.[1], Carbonaro, D.[3], Choi, Y.C.[3], Shaw, K.[3], Hershfield, M.[4], Wayne, A.[5], Kohn, D.[3], Candotti, F.[1 1] National Institutes of Health, Bethesda, MD; [2] Children's Hospital of Philadelphia, Philadelphia, PA; [3] Childrens Hospital Los Angeles, Los Angeles, CA; [4] Duke University Medical Center, Durham, NC; [5] National Institutes of Health, Bethesda, MD

We report on immune reconstitution in 3 patients (pts) who received GT× for ADA-SCID. After conditioning with 75 mg/m2 busulfan, pts received $2–5 \times 10^6$ autologous CD34+ bone marrow cells/kg that had been exposed to two retroviral vectors, MND-ADA and GCsapM-ADA. Chemotherapy was well tolerated, although in two pts, return of neutrophil counts was delayed. Post-transplant, indices of immunity improved or normalized. At 18 months after treatment, pt 301N's absolute lymphocyte counts (ALC's) have been up to ~600/μl (n.v. 2300–5400/μl). T-cell stimulation index (SI) to phytohemmaglutinin (PHA) and serum immunoglobulins and IgG subclass levels have normalized. In addition, the pt responded normally to tetanus, diphtheria, polio and haemophilus vaccines. Recently, he promptly recovered from a gram-negative central venous catheter infection. Pt 303N is 15 months after treatment and her ALC have been up to ~250/μl. PHA-SI and serum IgA levels have normalized, although the pt remains on IVIG. Pt 304C has been followed for 9 months. IgA has normalized, but other indices of immunity remain low. She resumed ADA enzyme replacement therapy after an episode of pneumonia. Nevertheless, her mononuclear cell ADA activity and percent corrected cells continue to increase. In all three pts, ADA activity has risen from less than 2 units to more than 30 units (n.v. 58–128 units), and toxic adenosine metabolites have fallen to levels comparable to those seen in pts who have engrafted after allogeneic hematopoietic cell transplant. Retroviral vector-marked cells in the peripheral blood vary from ~0.1% (301N) to 15% (303N) of the pts' circulating mononuclear cells. A fourth patient was treated on October 2, 2008, and is not yet evaluable. In summary, after treatment with myelosuppressive chemotherapy and bone marrow GTx, all 3 evaluable pts have shown improvement in laboratory indices of ADA activity and of immunity. Of the two pts who have been observed for more than a year off of PEG-ADA, one has had no infections and the other has answered two immunologic challenges as well as one would expect of a normal child. The results are in line with those reported by researchers in Italy and UK and indicate that gene therapy for ADA-SCID can lead to measurable improvement of immune function. While the degree of reconstitution is only partial when assessed in the laboratory, clinical responses to immunologic challenges appear to be robust.

66

AMBULATORY HEMATOPOIETIC STEM CELL TRANSPLANT (HSCT) FOR SEVERE PRIMARY IMMUNODEFICIENCY (PID) IN CHILDREN

Tse, W.T., Guarino, J., Schneiderman, J., Duerst, R., Jacobsohn, D., Chaudhury, S., Kletzel, M. Children's Memorial Hospital, Northwestern University Feinberg School of Medicine, Chicago, IL

Ambulatory HSCT has many potential benefits, but it is unknown if it will increase the risk of complications. We studied ambulatory HSCT in children with severe PID utilizing a reduced-intensity conditioning (RIC) regimen. In 2000–2008, 26 children with PID (SCID (n = 13), Hyper-IgM (4), Wiskott-Aldrich (2), XLPD (2), IPEX (2), Omenn (1), NEMO (1), Chediak-Higashi (1); median age, 0.6 year (range 0.1–17.4)) underwent HSCT after RIC (fludarabine 30mg/m2/day × 6; single-daily dose IV busulfan × 2, with targeted exposure based on area-under-the-curve (AUC) of a test dose; rabbit ATG 2mg/kg/day × 4). Patients received treatment and care primarily in an ambulatory setting. They were admitted for in-patient care if they had specific medical or psychosocial needs. Between transplant day -10 and +100, the median number per patient of scheduled clinic visits, acute care clinic visits and ER visits was 21 (range 0–27), 1 (0–4) and